REMARKS

It was noted in the Office Action that Applicants' amendments filed November 10, 2004, have been entered, but that only claims 6 to 21 are pending. Applicants' amendments filed November 10, 2004, contained new claims 22 and 23. Accordingly, Applicants believe that claims 6 to 23 are now pending in the application, and respectfully request clarification of the pending claims. The undersigned left a voicemail message for Examiner Hui on March 30, 2005, which was returned with the Examiner's voicemail of April 4, 2005, indicating that a new Office Action addressing claims 22 and 23 will be issued.

Claims 6, 7, and 10 are currently amended.

Claims 8 and 13 to 23 were previously presented.

Claims 9, 11, and 12 are original.

Claims 24 to 28 are new.

Claims 6 to 28 would be all of the claims pending in the application if the present amendments are entered.

Discussion of Claim Amendments

Claims 6 and 10 are currently amended to correct a typographical error in the second line. Claim 7, which depends from claim 6, is currently amended to delete compound names containing "sulfamoyl," as such compounds are not within the scope of claim 6. New claim 24 is added to claim the "sulfamoyl" compounds currently deleted from claim 7. Support for new claim 25 is found in the specification on page 16, in items (a), (c), (e), first (f), second (f), and (i). Support for new claim 26 is found in the specification on page 15, lines 1-21. Support for new claims 27 and 28 is found in the specification on page 23, lines 18-20.

Claim Rejections - 35 U.S.C. § 103

In the Office Action, Claims 6 to 21 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Scherle et al. (The Journal of Immunology, 1998;161:5681-5686) and McGilvray et al. (The Journal of Biological Chemistry,

1997;272(15):10287-10294) in view of Bridges (WO 98/37881). It was argued in the Office Action that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the MEK inhibitors of Bridges to treat arthritis such as osteoarthritis and rheumatoid arthritis. Allegedly, the inhibition of MEK was known to be involved in reducing the inflammatory process such as production of certain pro-inflammatory cytokines and prostaglandin E2 and interrupting the adhesion and recruitment of monocytes to inflammatory sites in the body.

Applicants respectfully traverse the rejection for each of the reasons provided below.

FIRST REASON:

Applicants repeat the arguments against the rejection that were made in their previous papers dated September 22, 2003, and November 8, 2004, which arguments are hereby incorporated by reference.

SECOND REASON:

Applicants believe that the skilled artisan would not have had a reasonable expectation of success for practicing the method of the present invention.

In the MPEP § 2143.02, the context for establishing a reasonable expectation of success for a method of treating a disease seems to be *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants believe that the court in *In re Merck* relied on the following teachings or suggestions in the prior art to establish that the skilled artisan would have had a reasonable expectation of success: (i) the close structural relationship between the prior art compound (imipramine), a known antidepressant, and the compound (amitriptyline) of Merck's invention method of treating depression, (ii) prior art ("Roche Reports") that recognized the structural relationship between imipramine and amitriptyline and concluded that amitriptyline should be tested for antidepressant activity, and (iii) the bioisosteric relationship between functional groups of imipramine and functional groups of amitriptyline.

Regarding the present rejection, Applicants believe that Scherle et al. discuss, among other things, a possible role of inflammatory mediators IL-1, IL-6, IL-8, and TNF-alpha in the context of the recruitment and activation of certain immune cells into sites of injury and infection (page 5681, column 1, first paragraph). Also, Scherle et al. disclose that U0126 blocks MEK activity with an IC_{50} of 70 nM whereas PD98059 has an IC_{50} of 5 μM (data not shown; page 5683, second column). In conclusion, Scherle et al. state:

> "Our results showing that U0126 inhibits cytokine and PGE_2 production by LPS-stimulated monocytes in vitro suggest that MEK inhibitors may also prevent inflammation in vivo. Based on these results, we have tested U0126 in several animal models of inflammation such as the carrageenan paw and TPA ear edema models and have demonstrated that the compound is efficacious (our unpublished data). Our data therefore demonstrate that MEK is another *potential* target for the design of therapeutic strategies in the treatment of inflammatory diseases" (page 5685, last paragraph; ***Emphasis added***).

Applicants believe that McGilvray et al. discuss, among other things, a possible role of the adhesion molecule VLA-4 in the context of monocyte recruitment in response to bacterial infection, tumor deposits, or atherosclerotic plaques (page 10287, second column, first full paragraph). McGilvray et al. also disclose that PD98059 is a selective MEK-1 inhibitor (page 10288, first column, EXPERIMENTAL PROCEDURES, *Buffers and Reagents*). In conclusion, McGilvray et al. state:

> "The present study is the first to describe a contributory role for the ERK pathway in the induction of adhesion-dependent inflammatory response in cells of monocyte/macrophage lineage. Since endothelial cell adhesion of monocytes via engagement of surface integrins is an early event in the mobilization of cells to sites of inflammation, it will be of interest to discern how inflammatory and anti-inflammatory mediator molecules acting via this or other signaling cascades might interact with

this activated pathway to modulate the inflammatory response" (page 10293, second column).

Bridges is directed to a method of treating septic shock, which relates to bacterial infection. Bridges also seems to disclose at least some of the compounds described in the present claims.

Applicants believe that there is no teaching or suggestion in Scherle et al. and McGilvray et al. taken in view of Bridges of treating arthritis, rheumatoid arthritis, or osteoarthritis *per se* with a MEK inhibitor, including a MEK inhibitor which is a compound of Formula I or II as described in the present claims.

Further, at the time of filing the present application, Applicants believe that the skilled artisan would have known that:

(i) Different inflammatory diseases affect different tissues, including the brain, heart, arteries, uterus, large and small intestines, skin, airway, lungs, or eyes;

(ii) Scherle et al. and McGilvray et al. disclosed that different "inflammatory diseases" have different causes such as injury, infection, tumor deposits, or atherosclerotic plaques; and

(iii) McGilvray et al. disclosed on, page 10293, second column, that there are other inflammatory signaling cascades besides the "ERK pathway," which involves MEK, suggesting that some inflammatory diseases do not involve MEK.

For example, encephalitis is an inflammatory disease of the brain, endocarditis is an inflammatory disease of the lining of the heart and its valves, pelvic inflammatory disease affects the uterus, fallopian tubes, and nearby structures, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis affect the intestines, an allergic reaction may produce inflammation of the skin, airway, lungs, or other organs, and conjunctivitis is an inflammatory disease of the eye. Examples of different causes include

atherosclerotic plaques, which may cause inflammation of the arterial wall and an eye infection, which may cause conjunctivitis of the eye.

For the reasons provided above, Applicants believe that there were sufficient reasons for the skilled artisan to believe treating inflammatory diseases was unpredictable and to reasonably doubt that a MEK inhibitor could successfully treat a specific inflammatory disease such as arthritis, rheumatoid arthritis, or osteoarthritis. These reasons include:

(i) The number of inflammatory diseases known,

(ii) The diverse causes of the inflammatory diseases,

(iii) The variety of tissues targeted by the inflammatory diseases,

(iv) The uncertainty of which inflammatory diseases would have been responsive to signaling cascades involving MEK, and

(v) The lack of a teaching or suggestion in Scherle et al. and McGilvray et al. taken in view of Bridges of treating arthritis, rheumatoid arthritis, or osteoarthritis with the MEK inhibitor of Formula I or II that is described in the present claims.

It is thus Applicants' belief that the skilled artisan would not have had a reasonable expectation of success treating arthritis, rheumatoid arthritis, or osteoarthritis with a MEK inhibitor.

THIRD REASON:

Applicants believe that an "obvious to try" standard has been used in the present rejection, which is not the standard for obviousness (MPEP § 2145(X)(B)).

Applicants believe that Scherle et al. and McGilvray et al. gave only general and uncertain guidance that MEK inhibitors might be useful for treating inflammatory diseases. As discussed above, Scherle et al. state: "Our data therefore demonstrate that MEK is another *potential* target for the design of therapeutic strategies in the treatment of inflammatory diseases" and McGilvray et al. state: ". . . it will be of interest to discern

how inflammatory and anti-inflammatory mediator molecules acting via this or other signaling cascades *might* interact with this activated pathway to modulate the inflammatory response" (*Emphasis added*). Applicants believe that Scherle et al. and McGilvray et al. were unsure if a MEK inhibitor could have been used to treat *any* inflammatory disease and, further, did not teach or suggest treating arthritis, rheumatoid arthritis, or osteoarthritis from among the *numerous inflammatory diseases* that were known to the skilled artisan.

It is Applicants' belief that the skilled artisan would have had to try each of numerous possible choices of inflammatory diseases until he or she possibly arrived at a successful result, but Applicants believe Scherle et al. and McGilvray et al. in view of Bridges gave no indication of which of many possible choices of inflammatory diseases were likely to be successfully treated with a MEK inhibitor.

Applicants believe that their teaching in Section D: Pharmacological Activity, beginning on page 73 of the specification, may have been used in hindsight to single out arthritis, rheumatoid arthritis, or osteoarthritis from among all of the inflammatory diseases that were known. Applicants respectfully believe that such a use of their disclosure is impermissible (MPEP § 2145(X)(A).

Accordingly, Applicants believe that claims 6 to 21 are not obvious over Scherle et al. and McGilvray et al. in view of Bridges, and are patentable under 35 U.S.C. § 103(a).

Conclusion

In view of the above amendments and remarks, Applicants believe that the rejection is overcome and request continued examination under 37 C.F.R. § 1.114 and reconsideration of claims 6 to 21 and consideration of claims 22 to 28.

Respectfully submitted,

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